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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,503	02/21/2001	Samuel J. Tremont	2045.40PCT/US	7558

5514 7590 03/04/2003

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EXAMINER
ZALUKAEVA, TATYANA

ART UNIT	PAPER NUMBER
1713	12

DATE MAILED: 03/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

AS-12

Office Action Summary	Application No.	Applicant(s)	
	09/647,503	TREMONT, SAMUEL J.	
	Examiner	Art Unit	
	Tatyana Zalukaeva, PhD	1713	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claim 15 has been amended in Paper No.12 to remove two types of covalent bonds between the polymer and the linker and leaving only N-C and P-C covalent bonds in place. Claims 19 and 20 has been amended to introduce new limitations. New claim 20 is added.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recited "form a substituent" is indefinite because it is not clear what is meant, apparently the connection is active ingredient---------→ linker------→ polymer, as understood from the claims and specification.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections of claim 15 under 35 U.S.C. 102(b) as anticipated by Ebert et.al. (Journal of Biomedical materials Research, Vol.16, 629-638, 1982) or Blossey et.al (J.Org Chemistry, 1990, 55,4664-4668). Or Sarobe et.al. (Polymers for Advanced Technologies, Volume 7, 749-753, 1996), or Severian et al (Reaserch Paper "Bioactive Polymers" 58 Chim OGGI, 09-1988, No.9, 59-63), **are withdrawn** due to an

amendment leaving **only N-C and P-C** covalent bonds between the linker and the polymer in place.

Ebert et.al. describe the immobilization of **prostacyclin (active ingredient)** on **a polymer** surface to ensure its sustained release over time. The procedure involves the use of **diaminoalkane spacer (linker) arm interposed between the polymer surface and immobilized active ingredient.**

In Materials and Methods section Ebert exemplifies a polymer chosen for immobilization as crosslinked polystyrene beds, which were further chlorsulfonated. The spacer was linked to preliminary prepared polymer , wherein the bonding between linker and polymer was confirmed by UV-Spectral analysis. After this stage was accomplished, the active ingredient, namely prostaglandin F2-alpha, was contacted with derivatized polymer to produce an immobilized (covalently bonded) physiologically active compound. The immobilized preparation showed improved release of an active ingredient versus time. The release of the said active ingredient which hag platelet aggregation inhibiting properties was due to its biodegradation (hydrolysis) of a covalent bond between the active ingredient and linker. **The covalent bond is S-N double bond**.

Blossey discloses drug delivery system wherein **dehydrocholic and cholic acid (active ingredient), attached via their carboxy group**, to chlormethylated polystyrene. Synthetic transformation of bound steroids containing carboxyl and

hydroxyl groups and esterification of hydroxyl was confirmed by ^{13}C NMR. A spacer, p-alkoxybenzoyl group, was used in conjunction with crosslinked polystyrene support and hydrochloic acid to obtain sustained-release preparation of hydrocholic acid. The NMR spectrum showd strong ssignals, characteristic of cross-linked polystyrene, containing hydroxymethyl groups. (Page 4664, col.2).

Experimental Section of the article provides specifics for chlomethylated crosslinked polystyrene, and spacer (Merrifield peptide resin), namely p-alkoxybenzyl (p.4667, col.1).On page 4668 Blossey exemplifies the delivery system which consists of polymer-spacer-dehydrocholate, which means it contains an active ingredient containing carboxyl functional group, a linker which is attached to an active ingredient via hydrolyzable covalent bond and a crosslinked polymer. In the instant case the bond between the linker and polymer **is an oxygen-carbon double bond**.

Sarobe teaches systems comprising an immunoglobulin G (active ingredient, **protein having carboxyl and amino groups**), covalently coupled to chloromethylstyrene beads. One of the best known in the art procedures for coupling of amino groups of protein to a polymer is via a reaction of the said protein with water soluble **carbodiimide** (linker). Sarobe utilizes polystyrene beads with chloromethyl functional groups, prepared by **covalent coupling of polystyrenes** (polymer) with chloromethyl containing moieties (linkers) , and thus afterwards providing a one-step reaction of chloromethyl group of derivatized polymer with amino group of protein molecules. (Page 749, col.2) In the systems prepared with chloromethyl functionality,

the attack of amino groups (in active ingredient molecule) on the chloromethyl groups of a polymer is governed by the diffusion of nucleophile. Severein discloses drug delivery systems. Scheme 1 on page 63 provides for a delivery system, wherein a metronidazole (an active ingredient) is bonded covalently to a copolymer of acrylic acid with styrene via an activator dicyclohexyl carbodiimide**. There is no covalent C-N or C-P bond between the linker and the polymer.**

5. Claims 15-20 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over WO 92/01477.

WO'477 discloses a drug delivery system which an active ingredient (abstract) , a linker and a polymer that is crosslinked, the acrive ingredient (drug) has active hydroxyl groups, ester groups, amino groups, carboxy groups, keto-enol groups etc (page 5, lines 5-12) . Polymeric material attached to a linker group. I this case the covalent bond is formed between an active ingredient and a linker group and a linker group in its own turn is attached to a polymer. (page 9, lines 10-20). Covalent bond between the linker and the polymer that can be cleaved under acidic conditions includes bonds of the following types: silyl ethers and esters, acetals, thioacetals, **imines (C-N bond), aminals, carbonates and vinyl estrs .** (page 9, lines 19-25). Polymers preferred by Tremont contain dimethylaminogroups (page 10, lines 1-20). The polymers may be crosslinked in order to render them insoluble under acidic conditions (page 10, lines 34, 35). The covalent bond between the drug and the linker is hydrolytically cleaved under

physiological conditions to release the effective amount of drug (page 11, lines 33-37). See also general schemes on pages 17-20.

Therefore the limitations of the instant claims are anticipated by WO'477.

In the alternative this rejection is made under 35 USC 103(a), since the reference teaches a small genus of linkers which places a claimed species in the possession of the public, ***In re Schaumann***, 197 USPQ 5, and the species would be obvious even if the genus were not sufficiently small to justify a rejection under 35 U.S.C. 102. Alternatively, the disclosure and claims provide the person of ordinary skill in the art with the motivation and a reasonable expectation of success to make and use the suggested C-N and C-P bonds between the linker and the polymer, and thus to arrive at the instant claims.

6. Applicant's arguments with respect to claims 15-19 have been considered but are moot in view of the new ground(s) of rejection.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tatyana Zalukaeva, PhD whose telephone number is (703)30-8819. The examiner can normally be reached on 9:00 - 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Wu can be reached on (703)308-2450. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0651.

TATYANA ZALUKAEVA
PATENT EXAMINER

Tatyana Zalukaeva, PhD
Primary Examiner
Art Unit 1713

February 26, 2003